transfer may effectively induce the overexpression of two immunosuppressive cytokines simultaneously and generate synergistic immunosuppression in cardiac allograft, and promote the cardiac allograft tolerance.

3:00 p.m.

409-5 **Treatment of Experimental Heart Failure With Hepatocyte Growth Factor**

Vasant Jayasankar, Timothy J. Pirolli, Lawrence T. Bish, Mark F. Berry, Joseph Woo, H. Lee Sweeney, Timothy J. Gardner, University of Pennsylvania School of Medicine, Philadelphia, PA

Background: Heart failure following myocardial infarction (MI) is a significant cause of morbidity and mortality and remains a difficult therapeutic challenge. Hepatocyte growth factor (HGF) is a potent angiogenic and anti-apoptotic protein whose receptor is upregulated following MI. This study was designed to investigate the ability of HGF to prevent the development of heart failure in a rat model of experimental MI. **Methods:** Rats underwent direct intramyocardial injection with replication-deficient adenovirus encoding HGF (n=7) or null virus as control (n=7) three weeks following ligation of the left anterior descending coronary artery. Analysis of the following was performed three weeks after injection: cardiac function by pressure-volume conductance catheter measurements, LV wall thickness, angiogenesis by Von Willebrand's Factor staining, and apoptosis by the TUNEL assay. The expression levels of HGF and the anti-apoptotic factor Bcl-2 were analyzed by Western blot. **Results:** Adeno-HGF treated animals demonstrated greater preservation of maximum LV pressure (HGF 77±2.9 vs Null 64±4.8 mm Hg, p=.04), maximum dP/dt (3024±266 vs 1907±360 mmHg/sec, p=.03), maximum dV/dt (133±20 vs 84±6 µl/sec, p=.04), and LV border zone wall thickness (1.98±.06 vs 1.53±.07 mm, p=.005). Angiogenesis was enhanced (151±10 vs 90±5 endothelial cells/hpf, p=.003), and apoptosis was reduced (3.9±0.3 vs 8.2±0.5%, p=.004). Increased expression of HGF and Bcl-2 protein was observed in the Adeno-HGF treated group. **Conclusions:** Overexpression of HGF three weeks post-MI results in enhanced angiogenesis, reduced apoptosis, greater preservation of ventricular geometry, and preservation of cardiac contractile function. This technique may be useful to treat or prevent post-infarction heart failure.

YOUNG INVESTIGATORS AWARDS COMPETITION

410 Young Investigators Awards Competition: Clinical Investigators

Monday, March 31, 2003, 4:00 p.m.-5:30 p.m.
McCormick Place, Room S104

4:00 p.m.

410-1 **Bone Marrow Derived Cardiomyocytes Are Present in Adult Human Heart**

Arjun Deb, Shaohua Wang, Kimberly Skelding, David Simper, Noel Caplice, Mayo Clinic, Rochester, MN

Background: Recent studies have identified cardiomyocytes of extracardiac origin in human hearts following gender mismatched cardiac transplantation but the exact source of these myocyte progenitors is currently unknown.
Methods: Hearts of female patients (n=4) who had undergone gender mismatched bone marrow transplantation (BMT) were recovered at autopsy and analyzed for the presence of Y-chromosome positive cardiomyocytes. Four female patients with gender matched BMT served as controls. Fluorescence in situ hybridization (FISH) for Y chromosome was performed on paraffin embedded sections to identify cells of bone marrow origin with concomitant immunofluorescent labeling for α-sarcomeric actin to identify cardiomyocytes.
Results: All patients with gender mismatched BMT were aged between 20 and 50 years at the time of death. The time duration from BMT to death varied between 5 weeks and 20 months. With the exception of one patient who had sudden death, all the others died from complications of BMT. A total of 16000 cardiomyocyte nuclei were analyzed approximating 2000 nuclei per patient. The mean percentage of Y chromosome positive cardiomyocytes in patients with sex mismatched BMT was 0.2 ± 0.12% with a range of 0.1%-0.4%. No evidence of inflammation was found in any of the hearts studied. Not a single Y chromosome positive cardiomyocyte was identified in any of the 6000 cardiomyocyte nuclei counted in control patients. Immunofluorescent co-staining for basement membrane laminin and chromosomal ploidy analysis with FISH showed no evidence of either pseudonuclei or cell fusion in any of the chimeric cardiac myocytes identified.
Conclusions: These data establish for the first time human bone marrow as a source of extra cardiac progenitor cells capable of de novo cardiomyocyte formation. The clinical significance of this finding will depend on further studies aimed at elucidating the mechanisms of mobilization, homing and differentiation of these cells.

4:15 p.m.

410-2 **High-Risk Clinical Features Predict Enhanced Post-Infarction Myocardial Apoptosis and the Need to Achieve Infarct-Related Artery Patency**

Antonio Abbate, Giuseppe G. Biondi-Zoccai, Rossana Bussani, Debora Camilot, Alessandro Petrolini, Furio Silvestri, Luigi M. Biasucci, Alfonso Baldi, Catholic University of Rome, Rome, Italy

Background. Infarct-related artery (IRA) patency after AMI is associated with favorable LV remodeling and beneficial clinical effects, in particular in patients with high risk features. As it has been reported that IRA patency is associated with reduced post-infarction apoptotic rate (AR), aim of our study was to assess whether IRA status had a different impact on AR in high- vs low-risk patients.
Methods. Co-localization for TUNEL and caspase-3 was used to calculate the AR at site of infarction at time of death in hearts of 30 subjects who died 10 to 62 days after AMI. Suitable positive and negative controls were performed. The Norris coronary prognostic index (NI) was calculated computing age, presence of pulmonary congestion, heart size and history of previous additional AMI, in order to define patients' individual risk at time of hospitalization. According to the NI (≤7 *vs.* >7), subjects were divided into low-risk and high-risk groups, since a NI>7 carries an approximate 3-fold higher short- and long-term risk of death after AMI.
Results. Twenty subjects (67%) had persistent IRA occlusion at time of death and in these patients AR was significantly higher than in those with open IRA (P<0.001). However the impact of IRA occlusion on AR was significantly different comparing high- vs low-risk subjects. In particular, AR was 10-fold higher in high-risk subjects with persistent IRA occlusion (26.1%[20.4-28.7%]) vs those with open IRA (2.3%[0.6-3.5%];P=0.002) and non-significantly different in low-risk subjects with vs those without IRA occlusion (8.2%[2.5-17.5%] vs 5.4%[1.5-7.9%];P=0.48).**Conclusions.** In high-risk subjects, a significantly higher AR is associated with persistent IRA occlusion late post AMI. The diverse impact of IRA occlusion on AR in subjects with different risk profile may explain the greater benefit obtained with coronary reperfusion in high-risk subjects, particularly those with LV dysfunction. The overall lower AR in low-risk subjects, however, may be correlated with the better long-term prognosis after AMI in this case, independently from the IRA status, suggesting the need to achieve IRA patency mostly in high risk patients.

4:30 p.m.

410-3 **Sensitivity of B-Type Natriuretic Peptide as a Noninvasive Screening Modality for Cardiac Allograft Rejection and Vasculopathy in Pediatric Heart Transplant Recipients**

Ilene Claudius, Yueh-Tze Lan, Ruey-Kang Chang, Glenn T. Wetzel, Juan C. Alejos, University of California, Los Angeles, Los Angeles, CA

Background: We sought to determine if B-type natriuretic peptide (BNP) levels are predictive of rejection or vasculopathy in children following orthotopic heart transplantation (OHT). BNP, an endogenous hormone produced in the ventricles, may serve as an alternative to endomyocardial biopsy and angiography for detecting rejection or transplant coronary artery disease (TCAD) in a select group of patients. Currently, no studies exist evaluating the sensitivity of BNP for identifying graft pathology in children.
Methods: We conducted a retrospective review of pediatric OHT patients who underwent catheterization, biopsy, and echocardiogram between January and June of 2002. A Mann-Whitney U test was used to compare the BNP levels in patients with evidence of pathology and those without. Sensitivity, specificity, and predictive value of BNP to detect cardiac pathology were also calculated using standard statistical methods.
Results: A total of 30 patients were studied, 8 patients with evidence of either rejection or TCAD, either clinically or by biopsy, angiography, and echocardiogram. We found a significant difference (p<.01) in BNP levels between patients with evidence of pathology and those without. Additionally, a BNP level of greater than 100 pg/mL had a 100% sensitivity (95% Confidence Interval: 68-100%) and a 100% negative predictive value (83-100%) for identifying any pathology in the transplanted heart. Specificity was 78% (60-90%) and positive predictive value 61% (36-82%).
Conclusions: BNP appears to be a highly sensitive test to identify pediatric OHT patients at risk for rejection or transplant coronary artery disease.

4:45 p.m.

410-4 **Prognostic Importance of Presenting Symptoms in Patients Undergoing Exercise Testing for Evaluation of Known or Suspected Coronary Disease: A Propensity Analysis**

R. Christopher Jones, Claire E. Pothier, Eugene H. Blackstone, Michael S. Lauer, The Cleveland Clinic Foundation, Cleveland, OH

Background: Chest symptoms, along with standard risk factors, are factored into pre-test risk stratification among patients who are candidates for stress testing. The independent pre- and post-test predictive values of symptoms are unclear.
Methods: We studied the outcomes of 10,870 patients referred for symptom-limited exercise testing who had no history of myocardial revascularization, heart failure, atrial fibrillation, or pacemakers. Symptoms were classified according to pre-specified definitions. Propensity analysis was used to account for selection biases and baseline differences.
Results: Symptoms of typical angina were present in 635 patients (6%), of atypical angina in 3,408 (33%), of non-anginal chest pain in 1,805 (17%), of dyspnea in 841 (8%),